Comments on the Proposed Listing of *Isoprene* in NTP's 9th Report on Carcinogens

Public Hearing
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Presented by

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for
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Today, my comments are being made on behalf of the IISRP which represents the majority of isoprene monomer and polymer producers in the world. Our member companies not only have a very substantial economic stake in the listing of this and other chemicals in NTP's carcinogen reports, but have also applied substantial financial and professional resources to the characterization and assessment of health risks associated with this product. We deeply regret that per NTP procedures, our input into this process consists of 5 minutes of oral testimony plus an invitation to present written comments on the "Background Document". In practice, the private sector is totally excluded from any scientific forums which could and should be held on these important matters.

Carcinogenicity

Less than one year ago, a rat NTP bioassay report was reviewed at this location which purported to demonstrate "clear evidence" of carcinogenicity. Many factors in that study suggested otherwise. The NTP used increases in benign tumors (mammary, testicular, renal sites) as support for "clear evidence". The explanation by NTP was that the sums of benign and malignant tumors were increased, and that was adequate support for the classification. It was also alleged that "there is good evidence that the benign tumors will progress to malignancies".

Response

- An increase in benign tumors is not one of the criteria listed by NTP as "clear evidence".
- NTP's bioassay report included no evidence or supporting data that the benign tumors seen in the rat isoprene study were of the type which progress to malignancies. Indeed, because the animals in the study were nearing the end of their lifetimes without indication of increased malignancies (despite benign tumor rates in excess of 50% at several sites), what stronger evidence could there be that these benign tumors are not likely to progress?
- To include "an increase of combination of malignant and benign tumors" as a criterion for "clear evidence" is scientifically unsound. This is axiomatic to suggesting that "benign tumor increases" are sufficient for "clear evidence". NTP has put this into practice, and if this is to continue as policy, it is suggested that this issue be placed into the toxicological arena for comment and review. This observation was recognized by certain members of this Subcommittee in 1997, and deserves serious attention.

For these reasons, the proposed use of rat tumorigenesis data as support for listing in the RoC is untenable.

Exposed Populations

The RoCs are to contain a list of carcinogens "to which a significant number of persons residing in the US are exposed." The NTP has not defined "significant number".

The NTP's bioassay report indicated that approximately 3700 individuals were exposed in industrial settings. However, this number appears to be high by a factor of 10 according to the assessment performed by IISRP. Our organization represents more than 90% of this industry, and is in an optimal position to accurately estimate isoprene-exposed worker populations. This information was submitted to NTP in June 1998, but is omitted from the Background Document.

In this country, there are only 2 isoprene monomer producers and perhaps 4-6 isoprene polymer producers. The following table presents data for potentially-exposed populations for 3 of the largest companies in this category.

Isoprene Monomer & Polymer Production

Company	# Production Employees
A	100
B	60
C	165
TOTAL	*325*

Job titles: process and lab technicians, column/stripper/reactor operators, polymer finishers, product loaders/shippers/warehousing

Of importance to the assessment of isoprene exposures are one direct and one indirect parameter. The first are measurements of isoprene concentrations in workplace air in the above described occupational settings during the last 5 years. The findings indicated that 81% of 426 air samples (4-hr or greater) were below 0.5 ppm, 91% were below 1 ppm, and 99% were less than 10 ppm.

The second parameter (as NTP correctly points out) that is likely to be associated with potential exposures is the isoprene monomer content of polymers. Very significantly, no isoprene monomer residuals were detected in isoprene-derived polymers at an analytical sensitivity of 0.1 ppm. Since these data were reported to NTP last June, Goodyear has improved its analytical sensitivity to 0.02 ppm. Analyses of polyisoprene (expected to contain highest monomer residuals) demonstrated that 89% of 19 samples had no detectable isoprene monomer while 100% had 0.04 ppm or less. If, as the Background Document suggests, "most exposures (of the 3700 in the "exposed" population) were to residual monomeric isoprene in polyisoprene products", the data for workplace air levels as well as negligible levels in polymer clearly demonstrate a lack of significant human exposure to this monomer.

Concluding Comments

Isoprene does not meet NTP criteria for listing in the 9th RoC based upon:

- The use of "clear evidence" of carcinogenicity in rats for listing is inappropriate due to the lack of support for this cancer classification in rats

- NTP has failed to consider data presented to it on numbers of isoprene-exposed individuals and the very low levels of workplace exposures to this monomer. That information plus demonstration that polymers contain negligible amounts of residual monomer show that "significant exposure" to this chemical does not occur in the US.
- Because of substantial numbers of factual errors in the Background Document, it is inappropriate to proceed on a RoC listing action at this time.